REMARKS

Status of the Claims

Pending claims

Claims 6, 7, 9 to 12, 21, and 23 to 36 are currently pending. In Applicants' response filed October 9, 2001, claims 4, 5, 8, and 22 were canceled; claims 6, 7, 21, and 23 were amended; and new claims 24 to 36 were added. Claims 9 to 12 were withdrawn from further consideration in Paper No. 9, in response to a restriction requirement by the Examiner.

Claims amended and canceled in the present amendment

In the present Response, claim 21 is canceled, and claims 24 to 27 to 30 and 34 to 36 are amended. Thus, after entry of the instant amendment, claims 6, 7, and 23 to 36 will be pending.

Outstanding Rejections

Pursuant to the Office Action, claims 7 and 24 are newly rejected under 35 U.S.C. 102(b) as allegedly anticipated by U.S. Patent No. 5,843,767, Beattie, issued Dec. 1, 1998 (hereinafter "Beattie"); claims 6, 23, 25, 26, 28 and 29 are newly rejected under 35 U.S.C. 102(e) as allegedly anticipated by U.S. Patent No. 6,083,763, Balch, filed Dec. 31, 1997 (hereinafter "Balch"); claims 6, 21, 23, 25 to 27 and 30 to 36 are newly rejected under 35 U.S.C. 102(e) as allegedly anticipated by U.S. Patent No. 6,101,946, Martinsky, filed Nov. 13, 1998, and having a priority date of Nov. 21, 1997) (hereinafter "Martinsky"); claim 7 is newly rejected under 35 U.S.C. 103(a) as allegedly unpatentable over Martinsky, as taught by a TeleChem International website copyright 1998, 1999, http://www.arrayit.com//products/solutions/mss/mss.html (hereinafter "TeleChem"); claims 21, 24, 27 and 30 to 36 are rejected under 35 U.S.C. 103(a) as allegedly unpatentable over Martinsky, as taught by TeleChem, in view of Beattie; claims 28 and 29 are rejected under 35 U.S.C. 103(a) as allegedly unpatentable over Martinsky, as taught by TeleChem, in view of Beattie as applied in claim 24 and further in view of Balch.

Applicants respectfully traverse all outstanding rejections of the claims.

Support for Claim Amendments

The specification sets forth an extensive description of the invention in the amended claims. Amended claim 24 merely incorporates the limitation of claims 27 and 28. Claims 27, 28, 29, 30, and 34 to 36 are amended in light of the amendment to claim 24. Support for methods for making biochips in which a binding agent is present only at the desired portions of the chip surface and is not present at portions where there is no probe can be found, inter alia, on page 8, lines 13 to 17; page 9, lines 1 to 7. No new matter has been introduced by the present amendment.

Issues under 35 U.S.C. §102

U.S. Patent No. 5,843,767, to Beattie

Claims 7 and 24 stand rejected under 35 U.S.C. §102(b) as allegedly anticipated by Beattie. Beattie is cited for allegedly disclosing a method for producing a biochip comprising providing a binding agent capable of immobilizing a probe to a biochip; spotting the binding agent to a plurality of positions on the biochip; and, spotting a plurality of probes onto the positions where the binding agent is spotted, thereby producing a biochip, citing column 13, line 51 to column 14, line 11.

The legal standard for anticipation under 35 U.S.C. §102 is one of strict identity. To anticipate a claim, a single prior source must contain each and every limitation of the claimed invention.

In paragraph 4, page 3, of the office action, the Patent Office noted that the Beattie was newly applied to claims 24 and 7 because the term "spotting" was given its broadest possible meaning, citing the Webster's Ninth New Collegiate Dictionary.

Applicants respectfully aver that method disclosed by Beattie does not comprise "spotting," even if the term is given its broadest meaning. As discussed in Applicants' response of October 9, 2001, Beattie's devices comprise a multiplicity of discrete and isolated regions, such as, e.g., a series of wells (see, e.g., Figs. 1 A, 2 to 4) or orifices (see, e.g., column 10, lines 35 to 44). Beattie's device is best described as an "array of orifices," or a "polymeric array of orifices" (see, e.g., column 10, lines 36 to 46). The wells, or orifices, are first coated with a binding agent (e.g., an epoxysilane if the bottom of the indentation is glass). In Beattie, to

deliver a binding agent, a "solution is flowed into the pores" of an orificed device (e.g., a glass wafer; see, e.g., column 13, lines 55 to 61). Beattie's intention is to coat the entire pore, including the walls of the pore, see, e.g., column 13, lines 46 to 49, and Example 4. Next, a biomolecule, e.g., a nucleic acid molecule, is attached (see, e.g., column 6, lines 21 to 26). As described in Example 4 (column 13), to affix a binding agent, it is "flowed into the pores."

Applicants respectfully aver that because Beattie's method, which pores binding agents into orifices or pores, does not disclose "spotting" even in the broadest meaning of the term, Beattie does not describe or suggest a method that "spots" a binding agent, such that when the probe is applied.

To address the Patent Office's concerns and to further clarify the distinguishing elements of the instant claimed methods over Beattie, claim 24 is amended to recite a method for producing a biochip comprising spotting a mixture of binding agent and probe on a plurality of spots, wherein the binding agent and probe is spotted with a pin or a tube (Claim 7 is dependent on claims 24, 25 and 26). Beattie does not teach or suggest a method for making a chip/ array using a pin or tube to spot a binding agent or a probe to a plurality of spots. Because Beattie does not teach each and every limitation of Applicants' claimed method, Applicants respectfully submit that claim 24 is not anticipated by Beattie. Furthermore, as claim 7 depends from claim 24 and incorporates all the limitations thereof, the method of claim 7 is also not anticipated by Beattie. Accordingly, Applicants request reconsideration and withdrawal of the rejection of amended claims 24 and 7 under 35 U.S.C. §102 as allegedly anticipated by Beattie.

U.S. Patent No. 6,083,763 to Balch

Claims 6, 23, 25, 26, 28 and 29 stand newly rejected under 35 U.S.C. 102(e) as allegedly anticipated by Balch (claims 6 and 23 are dependent on claim 26, claims 28 and 29 are directly or indirectly dependent on claim 26).

Regarding claims 25 and 26, the Patent office alleges that Balch discloses methods for producing a biochip comprising, inter alia, providing a mixture of a binding agent and a probe (*e.g.*, biotin derivatized nucleic acid and the attached probe), wherein said binding

agent is capable of immobilizing a probe to the biochip having a streptavidin film, citing column 6, lines 1 to 24 and column 18, lines 55 to 66 of Balch.[1]

The legal standard for anticipation under 35 U.S.C. §102 is one of strict identity. To anticipate a claim, a single prior source must contain each and every limitation of the claimed invention.

Claims 25 and 26 are drawn to a method for producing a biochip comprising spotting a mixture of binding agent and probe, wherein the binding agent is only provided on an area of the biochip where a probe is to be spotted. A binding agent is a substance that is capable of immobilizing a probe to a substrate surface, e.g., a plate. In Balch, the array surface immobilized streptavidin binds biotin-nucleic acid. Thus, the substrate surface immobilized streptavidin of Balch is a "binding agent." The methods of making arrays in Balch, which use a "streptavidin film," are distinguishable from the methods of claims 25 and 26, which expressly state that a binding agent is only provided on an area of the biochip or plate where a probe is to be spotted.

Accordingly, Balch does not teach or suggest spotting a mixture of binding agent and probe wherein the binding agent is only provided in an area of the biochip or plate where a probe is to be spotted. Therefore, claims 25 and 26 are not anticipated by Balch. Because claims 6, 23, 28 and 29 depend either directly or indirectly from claims 25 and 26 and incorporate all the limitations thereof, claims 6, 23, 28 and 29 are also not anticipated by Balch.

To address the Patent Office's concerns and to further clarify the distinguishing elements of the instant claimed methods over Balch, claims 25 and 26 are amended to recite methods for producing a biochip comprising a plurality of spots comprising probes in which the binding agent is present only at the desired portions of the surface and is not present at portions where there is no probe.

In light of the reasons provided above, Applicants respectfully request reconsideration and withdrawal of the rejection of claims 6, 23, 25, 26, 28 and 29 based upon 35 U.S.C. §102 as allegedly anticipated by Balch.

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[1] See page 4, lines 1-4 of the Office Action.

U.S. Patent No. 6,101,946 to Martinsky, as taught by TeleChem

Claims 6, 21, 23, 25 to 27 and 30 to 36 stand rejected under 35 U.S.C. 102(e) as allegedly anticipated by Martinsky, as taught by TeleChem (claims 6, 21, 23, 27 and 30 to 36 are directly or indirectly dependent on claims 25 and/or 26).

The legal standard for anticipation under 35 U.S.C. §102 is one of strict identity. To anticipate a claim, a single prior source must contain each and every limitation of the claimed invention.

The Patent Office alleged that Martinsky discloses a method for producing a biochip comprising providing a mixture of a binding agent (*e.g.*, Micro-Spotting Solution) and a probe wherein the binding agent is capable of immobilizing the probe to the biochip or plate and spotting the mixture to a plurality of positions on the biochip, wherein the binding agent is only provided on an area of the biochip where the probe is spotted, citing column 8, lines 51 to 58, of Martinsky.[2] It is alleged that TeleChem discloses a Micro-Spotting Solution comprising binding agents capable of immobilizing a probe to a biochip, citing page 2, Figure 1, of TeleChem.

Applicants respectfully aver that neither Martinsky nor TeleChem disclose a mixture of binding agent and probe to be spotted on a biochip or plate. Applicants respectfully aver that neither Martinsky nor TeleChem disclose a method for making a biochip comprising spotting a mixture of binding agent and probe to a plurality of spots, where the binding agent is present only at the desired portions of the surface and is not present at portions where there is no probe. Furthermore, the Micro-Spotting Solution does not a comprise a binding agent.

The paragraph comprising column 8, lines 51 to 58, of Martinsky cited by the Patent Office reads in full (to line 63 of column 8):

> The quality of the resultant microarrays depends on the printing surface and the buffer in which the samples are contained. The device herein has been used to print on sialylated microscopes slides purchased from CEL Associates (Houston, Tex.). A buffer that works well in conjunction with the sialylated microscope slides is a 1.times. concentration of Micro-Spotting Solution (TeleChem), which is a mixture of polymers and charged components. The device will also work well with biochemical compounds such as nucleic acids dissolved in standard buffers such as SSC and SSPE, which are available from a variety of vendors including Sigma. However, extremes in temperature or pH as well as the use of strong solvents may damage the pin's surface chemistry.

[2] See page 5, lines 13-17 of the Office Action.

Thus, the chip surface described by Martinsky is a sialylated microscope slide. The silane coated on the slide is a binding agent. Thus, the methods of Martinsky produce a biochip comprising binding agent on portions of the surface where there is no probe. Also, Martinsky notes that the Micro-Spotting Solution of TeleChem is a mixture of polymers and charged components.

Figure 1 of TeleChem, cited by the Patent Office, shows the effect of Micro-Spotting Solution on microarray quality. TeleChem does not disclose use of any binding agents. In addition, while the features of the TeleChem solution include supporting multiple printing technologies, improving micro-spotting consistency, increasing surface tension among other features, no mention of binding ability is provided. Moreover, in both the short and complete protocols, sialylated microscope slides are used. The silane coated on the slide is a binding agent. Sialylation is what binds the probe to the biochip.

Therefore, Martinsky, as taught by TeleChem does not disclose methods for producing a biochip comprising spotting a mixture of binding agent and probe to produce a plurality of spots comprising probes, where the binding agent is present only at the desired portions of the surface and is not present at portions where there is no probe, as expressly stated in the claimed methods. Accordingly, claims 25 and 26 are not anticipated by Martinsky, as taught by TeleChem. Because claims 6, 21, 23, 27 and 30 to 35 depend either directly or indirectly from claims 25 and/or 26, and incorporate all the limitations thereof, claims 6, 21, 23, 27 and 30 to 35, they are also not anticipated by Martinsky, as taught by TeleChem.

In light of the reasons provided, Applicants request reconsideration and withdrawal of the rejection of claims 6, 21, 25 to 27 and 30 to 35 based on 35 U.S.C. §102 as being anticipated by Martinsky, as taught by TeleChem.

Issues under 35 U.S.C. §103

Martinsky, as taught by TeleChem

Claim 7 stands rejected under 35 U.S.C. 103(a) as allegedly unpatentable over Martinsky, as taught by TeleChem International. Claim 7 depends from claims 24, 25 and 26 and incorporates all the limitations thereof.

For a proper rejection under 35 U.S.C. §103(a), the references, either alone or in proper combination, must teach or suggest all the claim limitations of Applicants' claimed invention.

As discussed above, Martinsky is defective in that it does not disclose methods for producing a biochip comprising spotting a mixture of binding agent and probe to produce a plurality of spots comprising probes, where the binding agent is present only at the desired portions of the surface and is not present at portions where there is no probe, as expressly stated in the claimed methods. The chip surface described by Martinsky is a sialylated microscope slide. The silane coated on the slide is a binding agent. Thus, the methods of Martinsky produce a biochip comprising binding agent on portions of the surface where there is no probe.

TeleChem does not cure the defect in Martinsky. TeleChem does not disclose or suggest methods for producing a biochip comprising spotting a mixture of binding agent and probe to produce a plurality of spots, where the binding agent is present only at the desired portions of the surface and is not present at portions where there is no probe, as expressly stated in the claimed methods. TeleChem's Micro-Spotting Solution does not comprise a binding agent. Because Martinsky in combination with TeleChem do not teach, suggest or motivate one skilled in the art to spot a mixture of binding agent and probe on a biochip or plate such that the binding agent is present only at the desired portions of the surface and is not present at portions where there is no probe, claim 7 is not rendered obvious by Martinsky, as taught by TeleChem.

Accordingly, Applicants request reconsideration and withdrawal of the rejection of claim 7 based upon 35 U.S.C. 103 as being unpatentable over Martinsky, as taught by TeleChem.

Martinsky, as taught by TeleChem, in view of Beattie

Claims 21, 24, 27 and 30 to 36 stand rejected under 35 U.S.C. 103(a) as allegedly unpatentable over Martinsky, as taught by TeleChem, in view of Beattie (claims 21, 27 and 30 to 36 are directly or indirectly dependent on claim 24).

The Patent Office alleges that Martinsky teaches a method for producing a biochip comprising providing a binding agent (*e.g.*, Micro-Spotting Solution) wherein the

binding agent is capable of immobilizing the probe to the biochip.[3] The Patent Office states that Martinsky is defective in that it does not teach that the binding agent is spotted prior to the step of spotting the probes.

Applicants agree that Martinsky is defective in that it does not teach that the binding agent is spotted prior to the step of spotting the probes because, in fact, the chip surface described by Martinsky is coated with binding agent. Martinsky uses a sialylated microscope slide. The silane coated on the slide is the binding agent. Thus, the methods of Martinsky produce a biochip comprising binding agent on portions of the surface where there is no probe.

TeleChem also does not teach a method wherein the binding agent is spotted prior to the step of spotting the probe. As discussed above, TeleChem does not disclose use of any binding agent. The Micro-Spotting Solution is not a "binding agent." It is the sialylation of the biochip that binds the probes to the biochip and not the Micro-Spotting Solution.

The Patent Office uses Beattie to cure the defects in Martinsky and TeleChem alleging that Beattie teaches a method wherein a binding agent is spotted onto the biochip prior to spotting the probe.

Applicants respectfully aver that method disclosed by Beattie does not cure the defects in Martinsky and TeleChem. The methods disclosed by Beattie do not comprise "spotting," even if the term is given its broadest meaning. As discussed above, Beattie's devices comprise a multiplicity of discrete and isolated regions, such as, e.g., a series of wells or orifices. Beattie's device is best described as an "array of orifices," or a "polymeric array of orifices". The wells, or orifices, are first coated with a binding agent. In Beattie, to deliver a binding agent, a "solution is flowed into the pores" of an orificed device. Beattie's intention is to coat the entire pore or orifice, including the walls of the pore or orifice. Next, a biomolecule is attached. To affix a binding agent it is "flowed into the pores."

Applicants respectfully aver that because Beattie's method, which pores a binding agent into orifices or pores, does not disclose "spotting" even in the broadest meaning of the term, Beattie does not describe or suggest a method that "spots" a binding agent, such that when

[3] See page 8, lines 7-9 of the Office Action.

the probe is applied. Accordingly, Beattie's disclosed method cannot cure the defects in Martinsky and TeleChem.

Furthermore, as Beattie and Martinsky/TeleChem teach a different method for producing a biochip, Applicants submit there is no motivation found in the references to modify the teachings of one with the other. However, even if one assumes, *arguendo*, that these references could be properly combined, as discussed above, they still would not teach each and every limitation of claim 24, as neither teach or suggest methods for spotting a binding agent to a biochip as in Applicants' claimed methods. Therefore, claim 24, as well as claims 30 to 36, which incorporate all the limitations of claim 24, are patentable over Martinsky, as taught by TeleChem, in view of Beattie.

Claim 27 has been amended to remove its dependency from claim 24, and claim 21 has been canceled, therefore, this rejection is moot as applied to those claims.

For the reasons stated above, Applicants respectfully request reconsideration and withdrawal of the rejection of claims 21, 24, 27 and 30 to 36 based on 35 U.S.C. §103 as being unpatentable over Martinsky, as taught by TeleChem, in view of Beattie.

Martinsky, as taught by TeleChem, in view of Beattie and further in view of Balch

Claims 28 and 29 are rejected under 35 U.S.C. 103(a) as allegedly unpatentable over Martinsky, as taught by TeleChem, in view of Beattie as applied in claim 24 and further in view of Balch. Claims 28 and 29 are directly or indirectly dependent on claim 24.

The Patent Office cites Martinsky, as taught by TeleChem, for the proposition that it teaches providing a binding agent (*i.e.*, Micro-Spotting Solution) and spotting the binding agent to a biochip.[4] As discussed previously, Martinsky does not teach, suggest or motivate one skilled in the art to provide a binding agent to be spotted to a biochip. Also discussed previously, Beattie does not teach, suggest or provide any motivation to spot a binding agent as contemplated in Applicants' claim 24. Balch, discussed previously, also does not teach, suggest, or provide any motivation for spotting a binding agent to the biochip or plate.

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[4] See page 10, lines 3-6 of the Office Action.

Accordingly, neither Martinsky, as taught by TeleChem, Beattie nor Balch, alone or in combination, teach or suggest each and every limitation of Applicants' claimed invention. Applicants request reconsideration and withdrawal of the rejection of claims 28 and 29 based upon 35 U.S.C. §103 as being unpatentable over Martinsky, as taught by TeleChem, in view of Beattie and further in view of Balch.

CONCLUSION

Claims 6, 7, 9 to 12, 21, and 23 to 36 are pending in the application. Claims 9 to 12 have been withdrawn from further consideration. Claim 21 has been cancelled and claims 24, 27, 28, 29, 30, 34 to 36 have been amended by the present Response. Applicants request that the Examiner reconsider the application and claims in light of the foregoing reasons and amendments and respectfully submit that the claims are in condition for allowance.

If, in the Examiner's opinion, a telephonic interview would expedite the favorable prosecution of the present application, the undersigned attorney would welcome the opportunity to discuss any outstanding issues and to work with the Examiner toward placing the application in condition for allowance.

Applicants believe that no fees are necessitated by the present Response. However, in the event any fees are due, the Commissioner is hereby authorized to charge any such fees to Deposit Account No. 06-1050.

Respectfully submitted,

Date: March 12, 2002

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VERSION WITH MARKINGS TO SHOW CHANGES MADE

Applicant : Ito et al. Art Unit : 1655
Serial No. : 09/451,666 Examiner : B.J. Forman, Ph.D.
Filed : November 30, 1999
Title : METHODS FOR PRODUCING BIOCHIPS (amended)

In the claims:

Claim 21 has been canceled, without prejudice.

Claims 24, 27 to 30 and 34 to 36 have been amended as follows:

24. (Amended) A method for producing a biochip comprising a plurality of spots comprising probes, the method comprising the following steps:

(a) providing a binding agent, wherein the binding agent is capable of immobilizing a probe to the biochip, and a probe;

(b) spotting the binding agent to a plurality of positions on the biochip; and

(c) spotting a plurality of probes onto the positions spotted in step (b), wherein the binding agent and the plurality of probes are spotted with a pin or a tube and the binding agent is only provided on an area of the biochip where a probe is to be spotted, thereby producing a biochip comprising a plurality of spots comprising probes in which the binding agent is present only at the desired portions of the surface and is not present at portions where there is no probe.

25. (Amended) A method for producing a biochip comprising a plurality of spots comprising probes, the method comprising the following steps:

(a) providing a mixture of a binding agent and a probe, wherein the binding agent is capable of immobilizing the probe to the biochip; and

(b) spotting the mixture to a plurality of positions on the surface of the biochip[;], wherein the binding agent is only provided on an area of the biochip where a probe is to be spotted, thereby producing a biochip comprising a plurality of spots comprising probes in which the binding agent is present only at the desired portions of the surface and is not present at portions where there is no probe.

26. (Amended) A method for producing a biochip comprising a plate comprising a plurality of spots comprising probes, the method comprising the following steps:

(a) providing a plate;

(b) providing a mixture of a binding agent and a probe, wherein the binding agent is capable of immobilizing the probe to the plate; and

(c) spotting the mixture to a plurality of positions on the plate[;], the binding agent is only provided on an area of the biochip where a probe is to be spotted, thereby producing a biochip comprising a plurality of spots comprising probes in which the binding agent is present only at the desired portions of the surface and is not present at portions where there is no probe.

27. (Amended) The method of [claim 24,] claim 25 or claim 26, wherein the mixture[, the probe or the binding agent] is spotted with a pin.

28. (Amended) The method of [claim 24,] claim 25 or claim 26, wherein the mixture[, the probe or the binding agent] is spotted with a tube.

29. (Amended) The method of claim 24 or claim 28, wherein the tube is a capillary tube.

30. (Amended) The method of claim 24 or claim 27, wherein the pin comprises a tip comprising at least one recess.

34. (Amended) The method of claim 24 or claim 27 [, claim 25 or claim 26], wherein the mixture, the probe or the binding agent is suctioned by the [a] pin and spotted on a plurality of positions on the biochip or the plate.

35. (Amended) The method of claim 24 or claim 27, [claim 25 or claim 26,] wherein the mixture, the probe or the binding agent is carried by a tip of the [a] pin and spotted on a plurality of positions on the biochip or the plate.

36. (Amended) The method of claim 24 or claim 27, [claim 25 or claim 26,] wherein the mixture, the probe or the binding agent comprises a solution, and the solution is carried by surface tension by a tip of the [a] pin and spotted on a plurality of positions on the biochip or the plate.